46. NON-SMOKING WIVES OF HEAVY SMOKERS HAVE A HIGHER RISK OF LUNG CANCER

*Kornegay HR, Kastenbaum MA, Mantel N, Harris JE, DuMouchel WH, MacDonald EJ, Hirayama T*
*Tobacco Inst., Washington, DC, 20006*
*Br Med J [Clin Res]; 283(6296):914-917 1981*

Critical questions concerning a previous report that Japanese wives of heavy smokers have a higher risk of lung cancer are posed. The criticisms include questions concerning statistical errors and information dealing with the groups studied. A reply clarifies some of the issues raised and concludes that the mortality from lung cancer in nonsmoking wives of smoking husbands is indeed significant. (1 Ref)

47. HEALTH HAZARDS ASSOCIATED WITH PASSIVE SMOKING?

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*Zentralinstitut fur Arbeitsmedizin, Adolph-Schonfelder-Str 5, D-200 Hamburg 76, W. Germany*
*MMW; 123(40):1485-1488 1981*

The results of two recent studies (by T. Hirayama and T. Garfinkel) concerning the association of passive smoking with lung cancer are critically evaluated. In both prospective studies, the incidence of lung cancer among women who do not smoke and who are married to men who do smoke was calculated. The results of the Hirayama studied indicated that such women have a significantly increased risk of developing lung cancer, while the results of the Garfinkel study indicated that the risks was slightly increased. Each study is discussed with regard to choice of test subjects, quantification of passive smoking, and statistical analyses used. The histological classification of the lung tumors in women in the Hirayama study is considered with respect to the known incidence of adenocarcinomas among women and the death of evidence suggesting a correlation between smoking and adenocarcinomas. It is concluded that no scientific evidence yet exists which proves that passive smoking increases the risk of development of lung cancer. (no Refs)

48. CONCLUSION: EXTENT OF SPECULATION

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*MMW; 124(4):19-20 1982*

Influence of passive smoking on health is reviewed. Air concentrations of dimethylnitrosamine (NDMA) and estimated NDMA concentrations in humans inhaled during 8 hr exposure to cigarette smoke are presented. According to presented data health hazards caused by inhalation of NDMA are speculative. (10 Refs)

49. HIRAYAMA'S DATA ARE NOT REPRESENTATIVE

*Heller WD*
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*MMW; 124(4):11-12 1982*

Causes of discrepancies in the data for lung cancer mortality rates (MR) in the female population of Japan are discussed. Only 40-yr-old and older females were studied but MR was evaluated for the whole female population, thus giving lower MR. (1 Ref)

50. UNSATISFACTORY STATISTICAL ASSURANCE

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*Institut fur Statistik und Mathematische Wissenschaftstheorie, Postfach 6380, D-7500 Karlsruhe 1, W. Germany*
*MMW; 124(4):15 1982*

Reliability of statistical studies on lung cancer (LC) risk for passive smokers is discussed. Significance of LC distribution for married nonsmoking female population according to smoking habits of husbands, and Mantel-Haenszel test are reviewed. Better statistical assurance is necessary to confirm the hypothesis of LC risk for nonsmokers. (no Refs)

51. CAUSAL RELATIONSHIP DOUBTFUL

*Grimmer G*
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*MMW; 124(4):16 1982*

Verification of a possible relationship between the concentration of carcinogens in cigarette smoke and increased lung cancer risk in nonsmokers is discussed. In a closed space carcinogens in cigarette smoke reach concentrations that could cause a significant enhancement of lung cancer incidence in nonsmokers, but statistical methods used to prove the relationship are doubtful. (1 Ref)

52. PREVALENCE AND CORRELATES OF PASSIVE SMOKING

*Friedman GD, Petitti DB, Bawol RD*
*Am J Public Health; 73(4):401-5 1983*

The duration per week of exposure to others' tobacco smoke in different locations was tabulated from the questionnaire responses of 37,881 non-smokers and ex-smokers who received multiphasic health checkups in 1979 and 1980. Altogether 63.3 per cent of subjects reported some exposure, 34.5 per cent were exposed at least 10 hours per week, and 15.9 per cent at least 40 hours per week. Duration of exposure per week was weakly correlated with serum thiocyanate level in a small test group. Exposure was strongly related to age with a peak of 78.2 per cent in the twenties decade and an accelerating decline thereafter to 13.9 per cent in those age 80 and over. Sex and race were related to passive smoking only to a relatively small degree. Persons reporting longer exposures were more apt to report greater use of alcohol and marijuana, exposure to occupational hazards, and being currently not married. Lack of college education was most frequent among those denying exposure but was directly related to exposure duration among those reporting some passive smoking. Studies of the health effects of passive smoking should take into account these associated factors. Although the reported passive smoking of married persons was strongly related to their spouses' habits, categorization by spouses' smoking resulted in considerable misclassification.

53. MISCLASSIFICATION OF ENVIRONMENTAL TOBACCO SMOKE EXPOSURE: ITS POTENTIAL INFLUENCE ON STUDIES OF ENVIRONMENTAL TOBACCO SMOKE AND LUNG CANCER

*Kilpatrick SJ Jr*
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*Toxicol Lett; 35(1):163-8 1987*

The effects of selection, confounding, misclassification and bias must be eliminated from case-control studies of 'passive smoking' and lung cancer before a meaningful interpretation can be made. Misclassification includes the misclassification of the subject's non-smoking status, of the disease status or of the spouse's smoking habits. This paper shows that inflation of the amount smoked by the husbands of female lung cancer cases may have accounted for the apparent 'dose-response' relationships in 3 widely referenced case-control studies.

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**54. LUNG CANCER AND PASSIVE SMOKING: ASSOCIATION OF AN ARTEFACT DUE TO MISCLASSIFICATION OF SMOKING HABITS?**

*Lee PN*

*Toxicol Lett; 35(1):157-62 1987*

1775 subjects were asked about their current use of tobacco products or nicotine chewing gum. 1537 provided a sample of saliva for cotinine analysis. Of 808 who claimed not to be users of such products, 20 (2.5%) had cotinine values above 30 ng/ml, suggesting their self-reports were false. In another study, 540 subjects were interviewed on two occasions. 10% of subjects claiming on one occasion never to have smoked made inconsistent statements on the other occasion. A third study showed a strong tendency for smokers to marry smokers. Bias caused by misclassification of smoking habits coupled with between-spouse smoking habit concordance can completely explain reported apparent excesses in lung cancer risk in non-smokers married to smokers.

**55. PASSIVE SMOKING AND LUNG CANCER ASSOCIATION: A RESULT OF BIAS?**

*Lee PN*

*Independent Consultant in Statistics and Epidemiology, Sutton, Surrey, UK.*

*Hum Toxicol; 6(6):517-24 1987*

1 Epidemiological studies have reported that non-smokers married to smokers have a lung cancer risk 20-50% higher than that of non-smokers married to non-smokers. 2 In contrast, extrapolation based on relative smoke exposure of passive and active smokers would predict a much smaller effect. 3 This paper examines the possibility that bias due to misclassification of smoking habits, coupled with between spouse smoking habit concordance, could account for this discrepancy. 4 One thousand seven hundred and seventy-five subjects were asked about their smoking habits and use of other nicotine products in a non-health context likely to minimize underreporting of smoking. One thousand five hundred and thirty-seven provided saliva for cotinine analysis. Of 808 who claimed not to be users of such products, 2.5% had cotinine values above 30 ng/ml, suggesting their self reports were false. In another study 540 subjects were interviewed in 1980 and in 1985. Ten per cent claiming on one occasion never to have smoked, made inconsistent statements on the other occasion. A third study showed a strong tendency for smokers to marry smokers. 5 Estimates of bias based on these data indicate that misclassification can explain the unexpectedly high lung cancer risk associated with spouse smoking in epidemiological studies of self-reported never smokers.

**56. LUNG CANCER FROM PASSIVE SMOKING: HYPOTHESIS OR CONVINCING EVIDENCE?**

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*Int Arch Occup Environ Health; 59(5):421-37 1987*

The epidemiological literature on passive smoking and lung cancer is reviewed and the well-known criteria for establishing a causal relationship are applied in order to determine what level of causal evidence currently exists. Three cohort studies and 12 case control studies are analysed. Of the prospective cohort studies, one contributes very little to our knowledge, one shows no risk increase and one results in a moderate risk increase of 1.74 for women married to heavy smokers. The last is the only study which has to be taken seriously, even when other considerations show that its results might be caused by chance, bias or confounding. None of the six case control studies yielding a positive relationship was conducted according to the state of art of epidemiological research, giving reasonable and sound evidence which cannot be explained by chance, bias, confounding or misclassification. Two studies contribute nothing to the evidence. None of the four case control studies yielding no risk change or a risk decrease can exclude the possibility that a causal relation exists. The epidemiological and toxicological evidence is discussed in the light of recent findings. The volume of accumulated data is conflicting and inconclusive. The observations on nonsmokers that have been made so far are compatible with either an increased risk from passive smoking or an absence of risk. Applying the criteria proposed by IARC there is a state of inadequate evidence. The available studies, while showing some evidence of association, do not exclude chance, bias or confounding. They provide, however, a serious hypothesis. Further studies are needed, if one wants to come to an adequate and scientifically sound conclusion concerning the question as to whether passive smoking causes lung cancer in man. (62 Refs)

**57. PASSIVE SMOKING AND LUNG CANCER: A PUBLICATION BIAS?**

*Vandenbroucke JP*

*Department of Clinical Epidemiology, University Hospital, Leiden, The Netherlands.*

*Br Med J [Clin Res]; 296(6619):391-2 1988*

To assess the likelihood of publication bias in a recent review of the effect of passive smoking on lung cancer the evidence from the reviewed papers was visualised on a 'funnel' plot. In such a plot if the relative risks from various studies are plotted according to sample size they should scatter round some underlying true value, the scatter being greatest where the studies have the lowest statistical power - thus showing a 'funnel' pattern. If there is publication bias and studies with non-significant results are not being published there should be a 'gap' in the plot. The logarithm of the relative risks was plotted against the standard error of the logarithm of the relative risk (which was used instead of sample size as a measure of statistical uncertainty). The resulting plot was compatible with a publication bias but only in studies on men. Further studies of passive smoking and lung cancer in men seem to be warranted.

**58. THE RELIABILITY OF PASSIVE SMOKING HISTORIES REPORTED IN A CASE-CONTROL STUDY OF LUNG CANCER**

*Pron GE, Burch JD, Howe GR, Miller AB*

*NCIC Epidemiology Unit, University of Toronto, Ontario, Canada.*

*Am J Epidemiol; 127(2):267-73 1988*

A test-retest design has been used to examine the reliability of passive smoking histories reported in personal interviews. A total of 117 control subjects initially interviewed in a lung cancer case-control study conducted in metropolitan Toronto, Canada, between 1983 and 1984 were reinterviewed on average six months later. Responses to initial screening questions used to detect a person's exposure to passive smoke were more reliable for residential than for occupational exposure. Respondents also more reliably reported residential exposure to spouse's passive smoke than to the passive smoke of others at home. Quantitative measures of exposure to passive smoke, i.e., number and duration of exposure, were even less reliably reported. Nonsmoking respondents gave the most reliable information. The low reliability of self-reported duration of exposure to passive smoke is consistent with the inability of several studies to detect a significant dose-response relation with lung cancer risk when measures of dose that depend solely on duration are used.

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59. PASSIVE SMOKING AND LUNG CANCER: CURRENT EVIDENCE AND ONGOING STUDIES AT THE INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

*Saracci R, Riboli E*
*International Agency for Research on Cancer, Lyon, France.*
*Mutat Res; 222(2):117-27 1989*

The evidence available from 3 cohort and 11 case-control studies investigating the relationship between exposure to environmental tobacco smoke (ETS) and lung cancer in non-smokers is reviewed. While it appears most likely that a causal relationship exists, the size of the effect, under different circumstances of exposures, remains to be accurately estimated. This requires studies using valid instruments (e.g., questionnaires) to quantitate exposures, and free as far as possible from biases. An investigation addressing this point is in progress under the coordination of the International Agency for Research on Cancer.

## II.

## *EXPERIMENTAL STUDIES ON THE BIOLOGICAL EFFECT OF SIDESTREAM TOBACCO SMOKE*

### A.

### Genotoxic Activities of Sidestream Tobacco Smoke

60. CYTOGENETIC EFFECTS OF TOBACCO SMOKE EXPOSURE AMONG INVOLUNTARY SMOKERS

*Sorsa M, Husgafvel-Pursiainen K, Jarventaus H, Koskimies K, Salo H, Vainio H*
*Institute of Occupational Health, Helsinki, Finland.*
*Mutat Res; 222(2):111-6 1989*

Tobacco smoke is highly genotoxic and produces chromosomal damage in several experimental systems. Active smokers have been shown to have an increased prevalence of somatic chromosome damage in their peripheral blood lymphocytes: this is seen in most cases as an increased sister-chromatid exchange (SCE) frequency and often also as increased structural chromosome aberrations (CAs). Among passive smokers, in association with exposure to environmental tobacco smoke, no such induction of chromosomal damage has been documented. In the present paper we report negative results on induction of chromosomal damage in 2 separate groups of intensive involuntary exposure to tobacco smoke, non-smoking restaurant personnel and newborn children of smoking mothers. While significant exposure in these groups is clearly seen in biochemical intake markers, e.g. cotinine and thiocyanate values in plasma, the conventional cytogenetic parameters, structural chromosome aberrations and sister-chromatid exchanges are unable to detect the low exposures of involuntary smokers.

61. GENOTOXICITY AND PAC ANALYSIS OF PARTICULATE AND VAPOUR PHASES OF ENVIRONMENTAL TOBACCO SMOKE

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*Mutat Res; 204(2):173-83 1988*

Samples of indoor air were collected from an office room (88 m3) both before smoking and during experimental smoking of 96 cigarettes by 10 persons within 6 h. The particulates were collected on glass-fibre filters and the vapour-phase compounds on XAD-2 resin. The samples were extracted with acetone and analysed quantitatively for polycyclic aromatic compounds and qualitatively with GC-MS. The extracts of filters and XAD-2 resins were fractionated into neutral/acidic and 2 basic (strong and weak bases) fractions; all these fractions were tested with the sister-chromatid exchange (SCE) assay in Chinese hamster ovary (CHO) cells and with the Salmonella/microsome test (strain TA98). Total concentrations of PAC were 205 ng/m3 in the background sample and 1207 ng/m3 after contamination by cigarette smoking. The total PAC concentrations were 4-6 times higher in the vapour phase than in the particulate phase. The fractions of the particulate samples collected before smoking showed mainly marginal genotoxic activity, whereas after smoking their genotoxicity increased dramatically. The fractions of the vapour phase samples were not genotoxic before smoking, but after smoking the neutral/acidic and strong basic fractions induced responses in both assays. The SCE assay was more sensitive towards the vapour-phase mutagens of environmental tobacco smoke (ETS). The relative responses of the two basic fractions, whereas the fraction containing neutral and acidic compounds was the most potent in the SCE assay. In the Salmonella test, the mutagenic activity was mainly detected with metabolic activation, while the induction of SCE in CHO cells was also seen without an exogenous metabolic activation system.

62. SISTER-CHROMATID EXCHANGE AND CELL PROLIFERATION IN CULTURED LYMPHOCYTES OF PASSIVELY AND ACTIVELY SMOKING RESTAURANT PERSONNEL

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*Mutat Res; 190(3):211-5 1987*

Sister-chromatid exchange frequencies were measured in peripheral lymphocytes of 12 cigarette smokers, 20 passive smokers, and 14 non-smokers with no regular exposure to tobacco smoke. All active and passive smokers worked as waiters and waitresses in restaurants. The passive smokers showed neither an increased mean SCE value nor an increased number of high SCE frequency cells (HFCs) when compared to non-exposed non-smokers. The incidence of SCEs and HFCs was observed to be elevated (P less than 0.01; P less than 0.05, resp.) among the active smokers. The proliferation rate of lymphocytes in whole blood cultures from the different exposure groups was also studied. The proportion of cells in first mitosis was lower and the mean replication index (RI) higher among the smokers than among non-smoker controls. However, no significant correlation was observed between the individual mean SCE and the replication index.

63. EFFECTS OF ALPHA-NAPHTHOFLAVONE ON LEVELS OF SISTER CHROMATID EXCHANGES IN LYMPHOCYTES FROM ACTIVE AND PASSIVE CIGARETTE SMOKERS: DOSE-RESPONSE RELATIONSHIPS

*Collman GW, Lundgren K, Shore D, Thompson CL, Lucier GW*
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*Cancer Res; 46(12 Pt 1):6452-5 1986*

The frequency of sister chromatid exchanges (SCE) were determined in lymphocytes of nonsmokers, passive smokers, and active smokers in the presence and absence of alpha-naphthoflavone (ANF). Higher levels of SCEs were detected for all smoking groups after in vitro addition of ANF when compared with an assay without ANF. There was a highly statistically significant difference between heavy smokers and nonsmokers (9.25 versus 7.43 SCE/cell) for the assay without

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ANF and for the ANF assay (14.2 versus 8.8). When considering the numerical difference in SCEs between the assays with and without ANF (delta SCE), higher values were noted for moderate smokers (2.7) and heavy smokers (4.9) compared to nonsmokers (1.4). Significant dose-response relationships were found between the frequency of SCEs and factors related to smoking, such as duration and frequency of cigarette use, tar, nicotine, carbon monoxide content of brand, and urinary measures of nicotine metabolites (cotinine and thiocyanate). No elevation of SCEs in passive smokers was found when compared to nonsmokers using either assay. The mechanism for SCE enhancement by ANF is unclear, but may be related to metabolic activation of the ANF by the cytochrome P-450 system in lymphocytes. The dosimetry relationships between cigarette smoke exposure and SCE frequency indicate that culture of human lymphocytes via ANF may provide a sensitive tool to detect exposure to cigarette smoke.

64. LIFE-STYLE AND CHROMOSOME DAMAGE; EFFECT OF PASSIVE SMOKING ON THE SISTER CHROMATID EXCHANGE FREQUENCY IN PERIPHERAL LYMPHOCYTES (MEETING ABSTRACT)

*Morimoto K, Miura K, Hoshi T*
*Dept. Public Health, Univ. Tokyo, Japan*
*Proc Annu Meet Jpn Cancer Assoc; 45:595 1986*

Life-style factors such as smoking and alcohol-drinking are known to have direct associations with high incidence of chromosome damage. Chromosome damage itself also has a close association with development of cancer. We had previously shown a significant increase of sister chromatid exchange (SCE) frequencies in peripheral lymphocytes from smokers as a function of the number of cigarettes consumed per day. We have here investigated the frequency of SCEs in passive smokers that had been working in coffee shops. The data indicate that there was no significant difference between the mean baseline-frequency of SCEs in peripheral lymphocytes from passive smokers and that in control persons, but that there was a significant difference of the mitomycin C-induced SCEs between these two groups of blood donors. The results also suggest that peripheral lymphocytes from passive smokers are hypersensitive to the chemical induction of SCEs.

65. HUMAN HEALTH SITUATION AND CHROMOSOME ALTERATIONS: SISTER CHROMATID EXCHANGE FREQUENCY IN LYMPHOCYTES FROM PASSIVE SMOKERS AND PATIENTS WITH HEREDITARY DISEASES

*Morimoto K, Miura K, Kaneko T, Iijima K, Sato M, Koizumi A*
*Department of Public Health, Faculty of Medicine, University of Tokyo, Japan.*
*Basic Life Sci; 29 Pt B:601-11 1984*

Lymphocytes from passive smokers, and patients with FA, Alz, or FPC were studied for SCEs in cultures treated with MMC, 4NQO, or MNNG. Fanconi anemia lymphocytes were also studied for cell cycle Tab. 3. Mean SCE frequencies in FPC or normal cells. (Table; see text) kinetics, and CAs after completion of 1, 2, or 3 or more divisions in MMC-treated cultures. The results can be summarized as follows: (1) lymphocytes from passive smokers showed a slightly higher induction of SCEs than nonsmokers when exposed to MMC. (2) FA cells had about 1.4 times higher frequencies of SCEs than normal cells in both MMC-treated and untreated cultures while they showed several times higher frequencies of CAs in both cultures. Analyses of cell cycle kinetics by the sister chromatid differential staining method revealed that MMC treatments of FA and normal cells led to a clearly dose-related delay in cell turnover times, the duration of delay being much longer in FA than in normal cells. (3) Alz cells showed about 1.5 times higher induction of SCEs in MMC-treated cultures whereas they had only 10% as much SCEs as controls when exposed to 4NQO. Familial polyposis coli cells showed no significant difference in the induction of SCEs in untreated cultures and cultures treated with MMC, 4NQO, and MNNG.

66. COMPARATIVE BONE MARROW CLASTOGENICITY OF CIGARETTE SIDESTREAM, MAINSTREAM AND RECOMBINED SMOKE CONDENSATES IN MICE

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*Mutagenesis; 3(5):419-22 1988*

The chromosome-damaging effects of cigarette sidestream (SS) and mainstream (MS) smoke condensates and a mixture of these were compared in 8-week-old NMRI mice by intraperitoneal administration. Each filtered commercial brand of cigarette was smoked by a smoking machine under the standard conditions, and the separately collected SS and MS smoke condensates were extracted with acetone/methanol as described elsewhere. The extracts were tested before and after treatment of animals with an enzyme inducer (Aroclor 1254) or inhibitor (Metyrapone). Increased formation of micronuclei within polychromatic erythrocytes (PCEs) of femural bone marrow 30 h after injection of the extracts was regarded as being due to a clastogenic effect. Regardless of the type of smoke extract injected, the increased formation of micronuclei was found to be dose dependent. The SS smoke condensate induced approximately 29% more micronuclei than the MS smoke condensate, the difference being significant (P less than 0.01). The overall clastogenicity of a 1:1 mixture of SS and MS smoke condensates was not substantially different from the activity of either SS or MS smoke condensate alone. Pretreatment of animals with Aroclor clearly enhanced the differences between the number of micronucleated PCEs caused by SS versus MS smoke condensate; SS smoke condensate induced 50% more micronuclei than did MS smoke condensate (P less than 0.001). Pretreatment of mice with Metyrapone did not modify appreciably the induction of micronuclei by either type of smoke. These results are discussed with reference to our previous data involving inhalation experiments and the recent issue of passive smoking.

67. CLASTOGENIC EFFECT OF PASSIVE SMOKING ON BONE MARROW POLYCHROMATIC ERYTHROCYTES OF NMRI MICE

*Mohtashamipur E, Norpoth K, Straeter H*
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*Toxicol Lett; 35(1):153-6 1987*

The genotoxic effect of passive inhalation of sidestream cigarette smoke on bone marrow polychromatic erythrocytes was studied using male NMRI mice. The animals were placed in individual 145.2-dm3 glass chambers resembling a room provided with normal air flow. They were exposed to the sidestream smoke of a commercial brand of cigarettes smoked by a smoking machine under standard conditions. Increased formation of micronuclei within polychromatic erythrocytes (PCEs) of femoral bone marrow 30 h after passive smoking was regarded as being due to the clastogenic effect of the smoke. Passive inhalation of the diluted sidestream smoke of a single cigarette resulted in a significant increase (P less than 0.01) in the frequency of micronucleated PCEs. This clastogenic activity was found to be dose-dependent.

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68. CONTRIBUTION OF POLYCYCLIC AROMATIC COMPOUNDS TO THE CARCINOGENICITY OF SIDESTREAM SMOKE OF CIGARETTES EVALUATED BY IMPLANTATION INTO THE LUNGS OF RATS

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*Biological Institute for Environmental Carcinogens, Grosshansdorf, F R G*
*Cancer Lett; 43(3):173-7 1988*

Particles and semivolatiles from sidestream smoke of cigarettes smoked on a smoking machine were collected by a filter combination consisting of a glass fibre filter and silanized polystyrene beads. The extract of the glass fibre filter was separated by a Sephadex LH-20 column chromatography into a fraction containing non-aromatic material plus polycyclic aromatic compounds (PAC) with 2 and 3 rings and a fraction consisting of PAC with 4 and more rings. To evaluate the carcinogenicity, both fractions as well as the semivolatiles were implanted into the lungs of Osborne-Mendel rats at a dose level of one cigarette per animal and compared with three dose levels of benzo[a]pyrene (BaP). The most pronounced carcinogenic effect of the sidestream smoke (100 ng BaP per cigarette) was caused by the fraction containing polycyclic aromatic hydrocarbons (PAH) with 4 and more rings (5 carcinomas of the lungs/35 rats). This fraction represents only 3.5% by weight of the total sidestream smoke condensate. By contrast, the semivolatile material did not provoke any tumors. Only a small contribution to the total carcinogenicity (1 carcinoma of the lungs/35 rats) was observed for the fraction containing non-aromatic material and 2- and 3-ring PAHs.

69. SELENIUM-MEDIATED REDUCTION IN THE MUTAGENICITY OF CIGARETTE SMOKE

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*Richard B. Russell Research Center, United States Department of Agriculture, Athens, Georgia 30613.*
*Environ Mol Mutagen; 11(3):369-78 1988*

Cigarette smoke contains carcinogens and mutagens and affects the health of smokers. Recently, increased research has proven the potentially protective activity of selenium (Se) against heavy metal toxicity, cancer, and other health disorders. Accordingly, we have proposed the fortification of tobacco with Se to develop safer cigarettes. As a start in evaluating any biological effects of added Se, we have determined the mutagenicity of inhaled, mainstream (MS) cigarette smoke condensate (CSC), with and without Se, in the preincubation assay of the Ames test. Initially, it was shown that Se, as sodium selenite, was not mutagenic at high concentrations (up to 80 micrograms/plate) with strains TA1538 and TA1978. Subsequently, the effects of different levels of Se, added to MS CSC, were examined with TA98, TA100, and TA1538. On the average, addition of 10 micrograms Se produced mutagenicity reductions of about 50%. Higher levels of added Se yielded further reductions. Cigarette sidestream (SS) smoke, collected between puffs, was also tested. Again, Se added to SS-CSC gave similar reductions, confirming its antimutagenic effect for both mainstream and sidestream smoke.

70. MUTAGENIC DETERMINATION OF PASSIVE SMOKING

*Ling PI, Lofroth G, Lewtas J*
*Department of Radiobiology, University of Stockholm, Stockholm, Sweden.*
*Toxicol Lett; 35(1):147-51 1987*

The mutagenic activity of tobacco smoke has been further investigated with the plate-incorporation method and a microsuspension technique of the Ames Salmonella assay. The microsuspension test gives a higher response than the conventional plate incorporation test. It is possible to detect environmental tobacco smoke (ETS) in moderately smoky indoor environments by collection of particulate matter with personal low volume samplers followed by particle extraction and mutagenicity testing with the microsuspension assay.

71. ENVIRONMENTAL TOBACCO SMOKE: COMPARATIVE CHARACTERIZATION BY MUTAGENICITY ASSAYS OF SIDESTREAM AND MAINSTREAM CIGARETTE SMOKE

*Lofroth G. Lazaridis G*
*Nordic School of Public Health, Gothenberg, Sweden.*
*Environ Mutagen; 8(5):693-704 1986*

Mainstream cigarette smoke particles were collected by means of a smoking machine, and sidestream particles were collected from the room in which the smoking took place. The particles were extracted by sonication with acetone, and the extracts were solvent-exchanged to dimethyl sulfoxide. The samples were tested for mutagenicity in the Ames Salmonella/microsome assay. The mainstream extract is preferentially mutagenic in the presence of S9, with about 30,000 revertants/cigarette in TA98, but has little or no activity in its absence. The sidestream extract is also mutagenic in the presence of S9 with TA98, and this activity is mainly due to basic compounds. Sidestream smoke is also significantly mutagenic in the absence of S9 in the strain TA100 as well as in TA97 and TA104. This 'direct' activity is due to components that are labile. The response of sidestream particles is 10,000-20,000 revertants/cigarette in TA98 + S9 and TA100-S9 when the collection is performed in a room where the particle concentration is modulated by deposition to surfaces. Sidestream particles collected on glass fiber filter and by electrostatic precipitation (ESP) with a commercial air cleaning device gave essentially the same mutagenic response, showing that ESP sampling may be an alternative to filter sampling for environmental tobacco smoke (ETS) in indoor environments. ESP sampling in children's rooms in smoking and nonsmoking homes showed that 5-10% of the tobacco smoke emitted in the smoking homes entered the child's room, demonstrating that diffusion of pollutants is faster than ventilation in modern buildings with low ventilation rates.

72. COMPARATIVE CARCINOGENIC POTENCIES OF PARTICULATES FROM DIESEL ENGINE EXHAUSTS, COKE OVEN EMISSIONS, ROOFING TAR AEROSOLS AND CIGARETTE SMOKE

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*Environ Health Perspect; 47:339-341 1983*

Mammalian cell mutagenesis, transformation and skin tumorigenesis assays show similar results in comparing the potencies of diesel, coke oven, roofing tar and cigarette smoke particulates. These assay results are reasonably consistent with the comparative carcinogenic potencies of coke oven and roofing tar emissions as determined by epidemiological studies. The bacterial mutagenesis assay tends to show disproportionately high potencies, particularly with diesel particulates. Results to date encourage the approach to the assessment for carcinogenic risks from diesel emissions based on the use of epidemiological data on cancer induced by coke oven emissions, roofing tar particulates and cigarette smoke with the comparative potencies of these materials determined by in vivo and in vitro bioassays. (Author abstract) (4 Refs)

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73. APPLICATION OF THE SALMONELLA MICROSOME TEST IN THE EVALUATION OF THE MUTAGENIC ACTIVITY OF CIGARETTE SMOKE: THE DIFFERENCE BETWEEN SIDESTREAM AND MAINSTREAM SMOKE

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*Ig Mod, 73(1):10-27 1980*

The mainstream and sidestream condensates from cigarette smoke were tested for mutagenic activity in Salmonella typhimurium strains TA98, TA100, TA1535, and TA1538. Mutagenic activity was found in both the basic and neutral fractions of crude condensates from mainstream and from sidestream smoke. All positive tests demonstrated a linear dose-response relationship. The findings indicate that for every cigarette smoked, the sidestream smoke is about 2 x more mutagenic than than the mainstream smoke. (12 Refs)

## B.

## Metabolism of Environmental Tobacco Smoke

74. NEW ASPECTS OF TOBACCO CARCINOGENESIS

*Hoffmann D, Melikian A, Adams JD, Brunnemann KD, Haley NJ*
*Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, New York 10595.*
*Carcinog Compr Surv; 8:239-56 1985*

In tobacco smoke, catechols represent a major group of co-carcinogens. Model studies have indicated that polyphenols and polysaccharides are two major groups of precursors for the catechol formation during smoking. Results from the application of BP together with catechol on mouse skin indicate that the detoxification path of BP metabolism is decreased and the formation of the BP-7,8-diol is increased in comparison to the metabolism pattern observed when BP is applied alone. It remains to be demonstrated that the increased BP-7,8-diol formation leads also to increased formation of BP-DNA adducts in epithelial tissues. The nicotine-derived N-nitrosamines represent a major group of carcinogens in chewing tobacco, snuff, and tobacco smoke. Their concentrations in processed tobacco and smoke exceed by far those of carcinogenic nitrosamines in other environmental materials. Whereas it has been shown that nicotine gives rise to NNN and NNK during tobacco chewing, the endogenous formation of these potent carcinogens upon smoke inhalation has so far not been demonstrated. However, the formation of N-nitrosoproline in cigarette smokers and snuff dippers proves that smoke and snuff have a measurable potential for the endogenous formation of carcinogenic nitrosamines. Finally, the data presented here indicate that the individuals subjected to passive smoke exposure under controlled conditions take up measurable amounts of particulate matter. The nicotine levels in the saliva of nonsmokers reflect recent passive smoke exposure and levels of nicotine and cotinine in urine reflect the long-term exposure to smoke particulates. The indicators, measured in saliva and serum, make it clear that uptake of particulates due to passive smoke exposure corresponds only to a low percentage (less than 2%) of the particulates that represent the uptake of a 1 pack-a-day adult smoker. However, in special settings, such as in the exposure of infants to the smoke pollutants generated by their mothers, uptake of smoke constituents can reach levels which raise concerns as to possible long range toxic effects. A broader base of subjects and a wider range of pollution situations need to be tested in order to substantiate the significance of the dosimetry of uptake executed to date. Such measurements constitute an attempt at more accurate risk assessment for nonsmokers in smoke polluted environments.

75. 32P-POSTLABELING TEST FOR SMOKING-RELATED DNA ADDUCTS IN ANIMAL AND HUMAN TISSUES

*Randerath K, Reddy MV, Avitts TA, Miller RH, Everson RB, Randerath E*
*Dept. of Pharmacology, Baylor College of Medicine, Houston, TX 77030*
*Banbury Rep; 23:85-98 1986*

A recently developed, highly sensitive 32P-postlabeling assay for the detection and quantitation of DNA adducts in animals and humans exposed to genotoxic chemicals was applied to studies of smokers' tissues. Among samples of placental DNA from 30 smokers, a single major adduct (adduct 1) was found in 29 samples. The adduct was found in 3/24 similar samples from nonsmokers. Of the three nonsmokers, who exhibited a very weak adduct 1 spot, two were passive smokers. Adduct 1 also was found in the DNA from other tissues of smokers, including lung parenchyma, aryepiglottic fold, and tonsils, but was not detectable in corresponding tissues of nonsmokers. Mouse skin DNA exposed in vivo to cigarette smoke condensate also gave adduct 1 as a predominant modified nucleotide. Preliminary experiments have excluded several polycyclic aromatic hydrocarbons and aromatic amines known to occur in tobacco smoke as the source of adduct 1. The chapter concludes with a discussion by conference participants. (24 Refs)

76. URINARY EXCRETION OF MUTAGENS IN PASSIVE SMOKERS

*Mohtashamipur E, Muller G, Norpoth K, Endrikat M, Stucker W*
*Institute of Hygiene and Occupational Medicine, University Medical Center, Essen University, F.R.G.*
*Toxicol Lett; 35(1):141-6 1987*

Six healthy young volunteers with no history of active smoking were asked to keep on their Western diets avoiding the consumption of alcoholic beverages, excess coffee, any sort of medicament, and the known pro- and/or anti-mutagen-containing foods and drinks, 24 h before and during the experiments. They were exposed passively to cigarette smoke produced by 4 habitual smokers in an unventilated 48.6 m3 room for 8 h. The carbon monoxide concentration was 18.85 +/- 7.3 ppm during the 8-h exposure. Frameshift mutagens were isolated from 10-h urine samples using chloroform and were tested for mutagenicity in the Salmonella/mammalian microsome assay employing Salmonella typhimurium TA98. Although clearly enhanced, no significant mutagenic activity could be found with 25 ml equivalent urine/plate after passive exposure to cigarette smoke. The weak mutagenicities found were highly significant when 50 ml equivalent urine/plate was tested. No direct correlation was observed between urine mutagenicity and the urinary cotinine concentration. The results obtained are discussed with reference to inconsistent reports in the literature concerning the mutagenicity of urine after passive smoking.

77. URINARY MUTAGENICITY AFTER CONTROLLED EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE (ETS)

*Scherer G, Westphal K, Biber A, Hoepfner I, Adlkofer F*
*Forschungsgesellschaft Rauchen und Gesundheit mbH, Hamburg, F.R.G.*
*Toxicol Lett; 35(1):135-40 1987*

20 non-smokers on a defined diet low in polycyclic aromatic hydrocarbons (PAH) were exposed to environmental tobacco smoke (ETS) in an unventilated room for 8 h. The urinary mutagenicity in the 24-h urine samples as tested with the Salmonella (TA98) microsome assay did not significantly increase after exposure to either 10 ppm CO or 20-25 ppm CO. We conclude that exposure of non-smokers to ETS does

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not lead to an increase in their urinary mutagenicity, provided the exposure conditions are within a realistic range.

### 78. EXCRETION OF MUTAGENS IN HUMAN URINE AFTER PASSIVE SMOKING

*Bos RP, Theuws JL, Henderson PT*
*Institute of Pharmacology, University of Nijmegen, The Netherlands.*
*Cancer Lett; 19(1):85-90 1983*

Eight non-smokers were experimentally exposed to cigarette smoke by staying in a poorly ventilated room together with heavy smokers for 6 h. Air samples were taken and the extract appeared to contain mutagenic substances. This is in accordance with the presence of carcinogens in tobacco smoke. Inhalation of the contaminated air by the passive-smokers resulted in an increase in the urinary excretion of products mutagenic in the Salmonella/microsome assay. This observation suggests that there is a causality in the association between increased cancer risk and passive-smoking, as was found by other investigators.

### 79. URINARY EXCRETION OF FRAMESHIFT MUTAGENS IN RATS CAUSED BY PASSIVE SMOKING

*Mohtashamipur E, Norpoth K, Heger M*
*Institute of Hygiene and Occupational Medicine, Essen University, Federal Republic of Germany.*
*J Cancer Res Clin Oncol; 108(3):296-301 1984*

Several male Wistar rats were individually placed in a chamber resembling a room provided with minimal air flow. They were exposed separately to the main- and sidestream smoke of a commercial brand of cigarettes smoked by a smoking machine. Exposure to both sidestream and mainstream smoke of at least two cigarettes resulted in significant excretions of frameshift mutagens in urine within 24 h, detected by the bacterial microtiter fluctuation test with Salmonella typhimurium TA1538. Doubling exposure to the mainstream smoke resulted in similar quantitative mutagenic activities. Doubling exposure to the sidestream smoke resulted in reduced water intake by the animals and thus toxic effects of the urine concentrates on the test bacteria.

### 80. HYDROXY-PHENANTHRENES IN THE URINE OF NON-SMOKERS AND SMOKERS

*Hoepfner I, Detthorn G, Scherer G, Grimmer G, Adlkofer F*
*Forschungsgesellschaft Rauchen und Gesundheit mbH, Hamburg, F.R.G.*
*Toxicol Lett; 35(1):67-71 1987*

Urinary hydroxy-phenanthrene (HO-PHE) excretion in non-smokers exposed to environmental tobacco smoke (ETS) is not increased. There is no significant difference in HO-PHE excretion between smokers (S) and non-smokers (NS), though excretion seems to be slightly elevated in smokers. A diet rich in polycyclic aromatic hydrocarbons leads to a rise in urinary HO-PHE excretion as compared to a diet low in polycyclic aromatic hydrocarbons (PAH), coming close to significance. HO-PHE excretion is not correlated with the mutagenic activity in urine.

### 81. PASSIVE AND ACTIVE EXPOSURE TO CIGARETTE SMOKE IN A SMOKING EXPERIMENT

*Sorsa M, Einisto P, Husgafvel-Pursiainen K, Jarventaus H, Kivisto H, Peltonen Y, Tuomi T, Valkonen S, Pelkonen O*
*Institute of Occupational Health, Helsinki, Finland.*
*J Toxicol Environ Health; 16(3-4):523-34 1985*

Six volunteer female habitual smokers were exposed during a 2-wk experimental period to cigarette smoke, both actively and passively, in an exposure chamber (volume 10 m3, average air exchange rate 6.8 times/h), where the ambient carbon monoxide, particle, and aldehyde concentrations were monitored. Three of the six subjects were smoking at the time, 2 cigarettes (filtered, self-burning low tar brand) per person per hour, 30 cigarettes altogether during each of the 5-h experimental days in the chamber. Samples of blood and urine were taken from each subject after 3 nonsmoking days and after each day of active or passive smoking. Among the parameters tested, blood carboxyhemoglobin, plasma cotinine, and urinary mutagenicity were higher in samples taken after active smoking than after nonsmoking periods. Although the exposure conditions were similar for all subjects, the parameters measured showed quite high interindividual variation. Thioethers and thiocyanates were not significantly elevated in the active smoking samples; neither were there any differences during this short experimental period in the sister chromatid exchange frequencies. The only parameters showing an increasing trend after passive exposure, as compared with nonsmoking samples, were urinary mutagenicity and plasma cotinine, the main metabolite of nicotine.

### 82. UPTAKE OF SIDESTREAM SMOKE BY SYRIAN GOLDEN HAMSTERS

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*American Health Foundation, Naylor Dana Institute for Disease Prevention, Valhalla, NY 10595.*
*Toxicol Lett; 35(1):83-8 1987*

An inhalation bioassay with Syrian golden hamsters is being conducted to evaluate the toxic and carcinogenic potential of cigarette sidestream smoke (SS) relative to mainstream smoke (MS). A Hamburg II smoking machine is used to deliver MS by nose-only exposure to hamsters and a modification allows for the simultaneous collection of SS for whole-body delivery to a different rack of animals. The tolerated dose of SS was determined by varying the air/smoke dilutions drawn through the animal restrainers. Preliminary data indicated that 20% carboxyhemoglobin (COHb) could be obtained in SS-exposed animals without fatality. Optimum exposure levels were determined. Monthly measurements of COHb, nicotine and cotinine indicate that the SS-exposed animals are absorbing slightly higher amounts of these smoke constituents than the MS-exposed hamsters. Tumor incidence and carcinogenicity data are being collected through complete necropsy and histology protocols and uptake data continue to be collected. These studies should help elucidate the carcinogenic potential of SS which has been suggested from its composition and from recent epidemiological data of cancer incidence in non-smokers.

### 83. ENDOGENOUS FORMATION OF N-NITROSOPROLINE UPON CIGARETTE SMOKE INHALATION

*Brunnemann KD, Scott JC, Haley NJ, Hoffmann D*
*Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, NY 10595.*
*IARC Sci Publ; 57:819-28 1984*

It was the goal of this study to assay the potential of inhaled cigarette smoke for endogenous N-nitrosation of amines in smokers by measuring urinary excretion of N-nitrosoproline (NPRO). Nonsmoking and smoking men were placed on a controlled diet which was low in proline and in ascorbic acid. On days 1-3, the volunteers received the controlled diet alone (Group I); on days 4-6, the diet was supplemented by a single daily dose of 300 mg proline (Group II); on days 7-9, the diet was supplemented by a single daily dose of 1 g ascorbic acid followed by 300 mg proline (Group III); and for the last three days, a single daily dose of 1 g ascorbic acid was given (Group IV). Collections of 24-h urine were made on days 3, 6, 9 and 12 of the study. The urine was analysed for NPRO, creatinine and cotinine. The mean 24-h NPRO excretion for 13 nonsmokers in Group I was 3.6 micrograms, whereas the NPRO excretion in 13 smokers was 5.9 micro-

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grams/24 h, significantly higher than that of the nonsmokers (p less than 0.05). Urinary NPRO in 14 nonsmokers of Group II was significantly lower than that of the 14 smoking volunteers (p less than 0.05). In Group III smokers had reduced urinary levels of NPRO as a consequence of ascorbic acid intake. Differences in NPRO excretion by smokers and nonsmokers in Group IV were insignificant. These findings suggest that the documented endogenous N-nitrosation of proline which occurs as a result of cigarette smoke inhalation may also apply to other N-nitrosatable amines, including nicotine, and thus lead to in-vivo formation of carcinogenic N-nitrosamines. Four nonsmokers exposed to passive smoke for 80 min three times per day did not exhibit elevated NPRO levels in their 24-h urine.

## C.
## Other Studies on the Biological Effect of Sidestream Tobacco Smoke

### 84. EFFECT OF SIDESTREAM AND MAINSTREAM SMOKE EXPOSURE ON IN VITRO INTERFERON-ALPHA/BETA PRODUCTION BY L-929 CELLS

*Sonnenfeld G. Hudgens RW*
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*Cancer Res; 46(6):2779-83 1986*

A peristaltic pump smoking machine that allows simultaneous generation of mainstream (active) and sidestream (passive) smoke from a cigarette was used to expose cultures of murine L-929 cells, a potent producer of interferon, to smoke. The cigarette used was the University of Kentucky 2R1 reference cigarette. The dosages of smoke used for exposure were the highest doses possible that generated a minimum toxic effect, and they were serially diluted to lower doses. Dosages were determined by the number of smoke puffs generated, the volume of smoke puffs generated, and the total particulate matter deposited on Cambridge filters in the smoke machine. Viability of exposed cells was equivalent to control cell cultures. Interferon-alpha/beta was induced by addition of polyriboinosinic-polyribocytidylic acid to the cells. Interferon production was substantially reduced in viable cells exposed to mainstream or sidestream smoke. Aging of smoke by delaying time of exposure of the cells to the smoke, or filtration of smoke through activated charcoal substantially decreased the alteration of interferon production by smoke exposure. These results suggest that actual exposure of cells to mainstream or sidestream smoke can inhibit in vitro interferon-alpha/beta induction, but the cells can be protected from these effects by smoke manipulation.

### 85. EFFECT OF SIDESTREAM TOBACCO SMOKE COMPONENTS ON ALPHA/BETA INTERFERON PRODUCTION

*Sonnenfeld G*
*Dept. Microbiology and Immunology, Univ. Louisville Sch. Medicine, Louisville, KY, 40292*
*Oncology; 40(1):52-56 1983*

Mouse embryo fibroblast cell cultures were treated with chemicals that are major components of sidestream (passive) cigarette smoke. These components were 4-aminobiphenyl and aniline-HCl. The cultures produced severely reduced levels of alpha interferon/beta interferon after challenge with polyriboinosinic-polyribocytidylic acid when compared to control cultures. Treatment of additional cell cultures with 2-methylquinoline, an intermediate-level component of sidestream tobacco smoke, or hydrazine-sulfate, a minor component of sidestream tobacco smoke but a major component of mainstream (active) tobacco smoke, also resulted in inhibition of interferon induction with polyriboinosinic acid-polyribocytidylic acid. Therefore, treatment of the cell cultures with chemicals that are carcinogenic was equally effective in inhibiting alpha/beta interferon induction without regard to the sidestream or mainstream smoke origin of the chemical. (Author abstract) (13 Refs)

### 86. EFFECT OF CARCINOGENIC COMPONENTS OF CIGARETTE SMOKE ON IN VIVO PRODUCTION OF MURINE INTERFERON

*Sonnenfeld G. Hudgens RW*
*Department of Microbiology and Immunology, University of Louisville School of Medicine, Kentucky*
*Cancer Res, 43(10):4720-2 1983*

Mice were treated with several different potentially carcinogenic components of tobacco smoke. The chemicals used were: 4-aminobiphenyl and aniline-HCl, which are found in high concentrations in sidestream tobacco smoke; hydrazine sulfate, which is found in high concentrations in mainstream tobacco smoke; and 2-methylquinoline, which is found in intermediate concentrations in both sidestream and mainstream smoke. The chemicals were injected i.p. into mice, and then alpha/beta interferon was induced in the mice by i.v. injection of polyriboinosinic-polyribocytidylic acid. The interferon was induced either 2, 24, or 48 hr after treatment with the tobacco smoke components. Mice treated with 4-aminobiphenyl showed some depression of interferon production 2 hr after treatment, maximum inhibition of interferon induction 24 hr after treatment, and a return to control levels of interferon 48 hr after treatment. Mice treated with hydrazine sulfate showed maximum inhibition of interferon induction 24 hr after treatment but no effects at any other treatment time. These components were the most carcinogenic chemicals of those utilized in this study. Treatment of mice with aniline-HCl, a chemical whose carcinogenic potential is still debated, resulted in marginal depression of interferon induction 24 hr after treatment. 2-Methylquinoline, the chemical with the lowest carcinogenic potential in this study, had no effect on interferon induction after administration to mice. In vivo interferon induction was, therefore, inhibited by treatment of mice with chemical carcinogens found in tobacco smoke. The efficacy of the chemical in inhibiting interferon induction was not influenced by the mainstream or sidestream smoke predominance of the chemical.

### 87. PULMONARY ARYL HYDROCARBON HYDROXYLASE ACTIVITY OF MICE, RATS AND GUINEA PIGS FOLLOWING LONG TERM EXPOSURE TO MAINSTREAM AND SIDESTREAM CIGARETTE SMOKE

*Gairola CG*
*Tobacco and Health Research Institute, Lexington, KY.*
*Toxicology; 45(2):177-84 1987*

Male, C57BL mice, Sprague-Dawley rats and Hartley guinea pigs were given daily exposure to either mainstream or sidestream whole smoke from University of Kentucky Reference cigarette, 2R1, for 16 weeks. Pulmonary aryl hydrocarbon hydroxylase (AHH) activity was assayed in lung tissue 9000 g supernatants by measuring the conversion of [3H]benzo[alpha]pyrene to its various metabolites. Both mainstream as well as sidestream smoke exposure increased the pulmonary AHH activity by approximately 3-4-fold over room and sham control rats and mice, but not guinea pigs. The magnitude of AHH induction in sidestream- and mainstream-exposed animals was similar, even though the dose of smoke particulates received by rats and mice in sidestream-exposed groups was significantly less than the amount inhaled by their corresponding mainstream-exposed groups. The data suggest that like mainstream, the sidestream ciga-

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rette smoke is also capable of inducing pulmonary AHH in responsive animal species.

88. SIDESTREAM CIGARETTE SMOKE-EXPOSURE OF MOUSE CELLS INDUCES CELL STRESS/HEAT SHOCK-LIKE PROTEINS

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*Toxicology, 39(3): 259-73 1986*

Specific alterations in cellular protein synthesis have been identified in mouse L929 and B16 cells exposed to 'passive' (sidestream) smoke freshly generated from unfiltered cigarettes. A decrease in both cell viability and protein synthesis was observed in monolayer cell cultures following exposure to increasing numbers (0-12) of puffs of sidestream smoke. With exposures that resulted in approximately 30% or higher loss in cell viability, there was an apparent induction of cell stress/heat shock-like polypeptides with approximate molecular weights of 88,000, 66,000 and 23,000. After exposure to higher numbers of puffs that led to a loss of cell viability of 80% or greater, a different set of polypeptides was synthesized, including a major new protein of 38,000 mol. wt and 2 other predominant proteins of 45,000 and 30,000 mol. wt. The same specific effects on cellular protein synthesis were also observed after exposure to a similar number of puffs of the gas phase of sidestream cigarette smoke (minus the particulate phase components).

89. AMMONIA EXPOSURE IN VITRO DEPRESSES MONOCYTE CYTOTOXICITY (MEETING ABSTRACT)

*Richman S, Tatum K, Stadig B, Richman K*

*University of Louisville School of Medicine, Louisville KY 40292*

*Proc Am Assoc Cancer Res; 24:829 1983*

We hypothesized that the potential immunotoxicity and cellular toxicity of tobacco smoke components might be screened using in vitro exposure of human peripheral blood monocytes to such compounds. We began by evaluating the effects of ammonia which is present in significant amounts in both sidestreamt and mainstream smoke. The effect of in vitro exposure to both NH4OH and NH4Cl on monocyte function was measured using K562 cells as a target for monocyte cytotoxicity as described by Fischer et al. The approximate dose of ammonia present in 1 cigarette (100 ug) was chosen as the starting amount/ml present during in vitro exposure. Heparinized blood from normal donors was placed on Ficoll-Hypaque gradients and the resulting mononuclear cell preparations allowed to adhere to plastic dishes coated with autologous serum. The monocyte enriched effector cells were recovered with Versene and cytotoxicity measured against Na251CrO4 labeled target cells in a 4 hr assay. Monocyte cytotoxicity was suppressed by exposure during the 4 hr assay to both NH4OH and NH4Cl. Exposure to 100 ug NH3 (as 5.9 mM NH4OH) depressed cytotoxicity from 18.4% to 4.6% in 8 normal donors. Exposure to 1.9 mM NH4Cl in 5 donors depressed cytotoxicity from 9.5% to 4.2%. These data may reflect the known suppressive effects of ammonia on lysosomal activity and may also be applicable to non-immune cells. (1 Ref)

90. THE ROLE OF VOLATILE AND NONVOLATILE N-NITROSAMINES IN TOBACCO CARCINOGENESIS

*Hoffmann D, Chen CH, Hecht SS*

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*Banbury Rep; 3:113-127 1980*

The role of tobacco-specific nitrosamines, both volatile (VNAs) and nonvolatile (NVNAs), in tobacco carcinogenesis is discussed. Analytical data for the major VNAs in the mainstream smoke of tobacco are presented. The VNA yield apparently depends on the nitrate content of the tobacco, the combustibility of the product, and the protein content of the tobacco. Studies have indicated that the VNA levels in sidestream smoke are significantly higher than in mainstream smoke. In general, commercial tobacco products contain between 1 and 2% of specific alkaloids, such as nicotine (90%), nornicotine, anatabine, anabasine, and cotinine. During curing and fermentation, tobacco-specific N-nitrosamines (NNAs), such as 4(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N'-nitrosonornicotine (NNN), are formed from alkaloids. Data indicating the relatively high concentration of tobacco-specific NNAs are presented. In mice, rats, and Syrian golden hamsters, NNN and NNK are proven carcinogens. Studies on the carcinogenicity of tobacco-specific NNAs are described. The metabolic activation of tobacco-specific NNAs and tobacco-specific NNAs in the saliva of tobacco chewers are also discussed. (37 Refs)

91. CARCINOGENIC EFFECT OF THE NITROSAMINES IN TOBACCO SMOKE

*Preda N, Bodor E*

*Sante Publique (Bucur); 29(3-4):233-9 1986*

Keywords (MeSH): English Abstract; Human; Lung Neoplasms/*chemically induced; Nitrosamines/*adverse effects; Smoke/*adverse effects; Tobacco Smoke Pollution/adverse effects; *Tobacco.

92. DEPOSITION OF SIDESTREAM CIGARETTE SMOKE IN THE HUMAN RESPIRATORY TRACT

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*Am Rev Respir Dis; 125(4):406-408 1982*

Measurement of deposition of sidestream cigarette smoke in the human respiratory tract is important for assessing the health effects of sidestream cigarette smoke. We measured the deposition fraction of sidestream cigarette smoke in five normal adult male volunteers using sidestream smoke at a concentration similar to that encountered indoors with smokers present. The mean deposition was 11%. These data indicate that the deposition fraction of sidestream smoke is similar to other previously studied aerosols in the same size range and is much less than mainstream smoke. (Author abstract) (14 Refs)

93. [PHYSIOLOGY AND HYGIENE OF SMOKING. 17. IN VIVO EFFECTS OF PASSIVE SMOKING (4). ITS RELATIONSHIP TO LUNG CANCER]

*Asano M*

*Kangogaku Zasshi; 46(12):1413-6 1982*

Keywords (MeSH): Human; Lung Neoplasms/*etiology; *Tobacco Smoke Pollution.

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# III.

# *MONITORING OF ENVIRONMENTAL TOBACCO SMOKE EXPOSURE*

## A.

## CHEMICAL ANALYSIS OF INDOOR TOBACCO SMOKE POLLUTION

### 94. AH RECEPTOR LIGANDS IN TOBACCO SMOKE

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*Toxicol Lett; 42(2):131-6 1988*

Tar particulates from cigarette smoke contain compounds with affinity for the Ah receptor. The sidestream activity is larger than that of the mainstream with a ratio of about 5. The compounds causing the affinity appear in the neutral fraction after chemical fractionation excluding basic and acidic components as major contributors to the affinity. The affinity cannot be explained by benzo[a]pyrene and other polycyclic aromatic hydrocarbons but it might be caused by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds and by oxidized tryptophan derivatives.

### 95. TOXIC AND CARCINOGENIC AGENTS IN UNDILUTED MAINSTREAM SMOKE AND SIDESTREAM SMOKE OF DIFFERENT TYPES OF CIGARETTES

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*Carcinogenesis; 8(5):729-31 1987*

The mainstream and sidestream smoke of four types of popular US cigarettes were analyzed for toxic and carcinogenic agents. The cigarettes included one without a filter tip, and one filter cigarette each with medium, low and ultra-low smoke yields. The analyses clearly demonstrated that 12 toxic agents determined in this study were significantly reduced in the mainstream smoke of filter cigarettes, as compared with smoke yields from the nonfilter cigarette. In the case of the ultra-low yield cigarette, mainstream smoke emissions were reduced by about 90%. In contrast to this finding, the emissions of the same toxic and carcinogenic components into sidestream smoke of the filter cigarettes were not greatly reduced. Sidestream smoke is the major contributor to environmental tobacco smoke, to which both smokers and nonsmokers are exposed. Although the exposure of the smoker to mainstream smoke components is decreased due to proportionally greater consumption of low and ultra-low yield cigarettes, and lower rates of consumption of cigarettes with high smoke yields, the carcinogenic potential of indoor pollutants originating from tobacco products is not diminished.

### 96. CHEMICAL CARCINOGENS IN TOBACCO

*Hoffmann D, Wynder EL, Hecht SS, Brunnemann KD, LaVoie EJ, Haley NJ*
*Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, NY 10595*
*Cancer Risks. Strategies for Elimination. Bannasch P, ed. New York. Springer-Verlag, p. 101-13, 1987.*

Chemical carcinogens in tobacco are discussed in relation to the problem of prevention of cancer through identification and reduction of the active agents in tobacco. Inhalation studies conducted with Syrian golden hamsters exposed to whole cigarette smoke, and bioassays of smoke condensate on mouse skin, have clearly demonstrated that a significant reduction of particulate matter and of polycyclic aromatic hydrocarbons leads to a concomitant reduction in the tumorigenic potential of cigarette smoke. Although changes in cigarette manufacturing techniques have been made in response to such studies, they are not considered adequate because (1) cigarette smokers may smoke more when yield of certain constituents is reduced, and (2) protection for organs other than the lungs from these measures has not been established. Also, the health benefits from cessation of smoking far exceed those available from changing the characteristics of the cigarettes. Nicotine and other cigarette components are precursors of the tobacco-specific nitrosamines (TSNA), which have been shown to induce the formation of the promutagenic adducts O6-methylguanine and O4-methylthymidine. It is likely that nicotine is endogenously N-nitrosated, leading to nitrosamines that add to the body burden of TSNA in the tobacco consumer. The measurement of nicotine and cotinine does not reflect the uptake of tobacco carcinogens per se since it is possible that nicotine and other tobacco alkaloids are precursors to endogenously formed TSNA. Epidemiological methods may never be sensitive enough to establish a low risk factor for involuntary smoking with sufficient significance, but biochemical data will clarify some of the current uncertainties with respect to the increased risk of cancer from passive smoking. Such data will include the measurement of absorption of tobacco carcinogens, their retention, and activation to reactive species by nonsmokers and knowledge on the repair of the miscoding properties induced in DNA by tobacco constituents. (55 Refs)

### 97. CHEMICAL CONSTITUENTS AND BIOACTIVITY OF TOBACCO SMOKE

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*IARC Sci Publ; (74):145-65 1986*

Tobacco smoke contains more than 3900 constituents. In this presentation we have summarized our present knowledge as to the physicochemical nature of tobacco smoke and specific agents therein. Emphasis has been placed on the discussion of formation and identification of toxic and, especially, of tumorigenic agents in tobacco smoke. In the concluding Table 13 we have listed those smoke constituents in the mainstream smoke of cigarettes that we regard as important contributors to the toxic and carcinogenic potential of tobacco smoke. This judgement is based on extensive laboratory studies. Finally, data are presented in support of the concept that product modification can reduce the carcinogenic potential of cigarettes. However, it must be emphasized that the only safe way to avoid the cancer risks associated with smoking is to refrain from smoking.

### 98. INDOOR AIR POLLUTION BY SMOKE CONSTITUENTS - A SURVEY

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*Prev Med; 13(6):570-81 1984*

A review of the literature on the present state of knowledge about the topic 'indoor air pollution by smoke constituents' has been made. While consideration is given to standard bibliographic works and more recent reviews, an evaluation of the results of field studies and experimental investigations carried out under realistic conditions is also made. The selection of the tobacco smoke constituents discussed here was based on environmental and toxicological aspects. The following substances are considered in detail: carbon monoxide, nitrogen oxides, formaldehyde, acrolein, ammonia, phenol, hydrogen cyanide, sulfur dioxide, cadmium, nickel, nicotine, some volatile nitrosamines, polycyclic aromatic hydrocarbons,

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and respirable particulates. The smoke constituent concentrations in the literature are presented in tables. The results are evaluated and discussed with respect to the maximum allowable concentrations presently valid in the Federal Republic of Germany. (52 Refs)

99. TOBACCO SMOKE IN THE WORKPLACE: AN OCCUPATIONAL HEALTH HAZARD

*Collishaw NE, Kirkbride J, Wigle DT*
*Department of National Health and Welfare, Ottawa.*
*Can Med Assoc J 131(10):1199-208 1984*

Tobacco smoke, which contains over 50 known carcinogens and many other toxic agents, is a health hazard for nonsmokers who are regularly exposed to it while at work. Involuntary exposure to tobacco smoke annoys and irritates many healthy nonsmokers. Serious acute health effects are probably limited to the one fifth of the population with pre-existing health conditions that are aggravated by exposure to tobacco smoke. The consequences of long-term exposure include decreased lung function and lung cancer. Existing air quality standards for workplaces do not directly specify an acceptable level for tobacco smoke. The evidence on the composition of tobacco smoke and on the health hazards of involuntary exposure suggests that there may not be a 'safe' level for such exposure.

100. INDOOR AIR POLLUTION, TOBACCO SMOKE, AND PUBLIC HEALTH

*Repace JL, Lowrey AH*
*Environmental Protection Agency, Washington, DC, 20460*
*Science; 208(4443):464-472 1980*

An experimental and theoretical investigation is made into the range and nature of the exposure of the nonsmoking public to respirable suspended particulates from cigarette smoke. A model incorporating both physical and sociological parameters is shown to be useful in understanding particulate levels from cigarette smoke in indoor environments. Observed levels of particulates correlate with the predictions of the model. It is shown that nonsmokers are exposed to significant air pollution burdens from indoor smoking. An assessment of the public health policy implications of these burdens is presented. (Author abstract) (53 Refs)

101. ON THE ANALYSIS OF 1-NITRONAPHTHALENE, 1-NITROPYRENE AND 6-NITROCHRYSENE IN CIGARETTE SMOKE

*el-Bayoumy K, O'Donnell M, Hecht SS, Hoffmann D*
*Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, NY 10595.*
*Carcinogenesis; 6(4):505-7 1985*

A method was developed for the analysis of 1-nitronaphthalene, 1-nitropyrene, and 6-nitrochrysene in mainstream cigarette smoke, using [14C]1-nitronaphthalene, [14C]1-nitropyrene, and [14C]6-nitrochrysene as tracers and internal standards. Cigarette smoke condensate was collected and the appropriate fractions containing the labelled standards were obtained by a series of solvent partitions and column chromatography. Recovery of internal standards ranged from 60 to 70%. The fractions were analyzed by capillary gas chromatography with electron capture detection and by combined capillary gas chromatography-mass spectrometry. 1-Nitronaphthalene (less than 10 ng/cigarette), 1-nitropyrene (less than 10 ng/cigarette), and 6-nitrochrysene (less than 1 ng/cigarette) were not detected in the mainstream smoke of the University of Kentucky 1R1 cigarette, a US commercial 85 mm non-filter cigarette, or a French commercial 70 mm non-filter cigarette.

102. IDENTIFICATION AND ANALYSIS OF A NEW TOBACCO-SPECIFIC N-NITROSAMINE, 4-(METHYLNITROSAMINO)-4-(3-PYRIDYL)-1-BUTANOL

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*Division of Environmental Carcinogenesis, Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, NY 10595.*
*Carcinogenesis; 8(3):465-9 1987*

A new tobacco-specific N-nitrosamine, 4-(methylnitrosamino)-4-(3-pyridyl)-1-butanol (iso-NNAL) was isolated from snuff tobacco. Structural characterization of this N-nitrosamine was confirmed by mass spectral analysis. Five popular US brands of moist snuff and three popular US brands of dry snuff tobacco were analyzed for moisture, nicotine and tobacco-specific N-nitrosamines. The moisture content varied from 20 to 53% in moist snuff and from 4.7 to 5.6% in dry snuff. The nicotine levels in these samples varied from 0.6 to 3.2%. The newly identified iso-NNAL was present in concentrations ranging from 0.07 to 2.5 p.p.m. whereas other tobacco-specific N-nitrosamines, N-nitrosonornicotine, N-nitrosoanatabine, N-nitrosoanabasine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone were found to range from 0.1 to 178 p.p.m. Iso-NNAL was not detected in mainstream and sidestream smoke of cigarettes. Iso-NNAL is genotoxic in primary rat hepatocytes; its tumorigenic properties are currently being tested in mice and rats.

103. ANALYSIS OF VOLATILE N-NITROSAMINES IN MAINSTREAM AND SIDESTREAM SMOKE FROM CIGARETTES BY GLC-TEA

*Brunnemann KD, Fink W, Moser F*
*Res. Div., Philip Morris Europe, CH-2003 Neuchatel, Switzerland*
*Oncology; 37(4):217-222 1980*

Volatile N-nitrosamines were quantitatively determined in mainstream and sidestream smoke of commercial cigarettes using gas chromatography-thermal energy analysis (GLC-TEA). The smoke was trapped in ascorbic acid soln buffered at pH 4.5 and then extracted with dichloromethane; the organic phase was chromatographed on basic alumina and analyzed by GLC-TEA. The mainstream smoke of 22 different commercial cigarettes from Germany and Switzerland contained between 0.1 and 27 ng dimethylnitrosamine (DMN), 1.5 and 29 ng nitrosopyrrolidine (NPY) and traces of methylethylnitrosamine (MEN). The sidestream smoke of these cigarettes contained between 143 and 415 ng DMN, 3.1 and 26 ng MEN and 28 and 150 ng NPY. In a final experiment we measured the DMN concentration in a sealed experimental chamber as a function of the number of cigarettes smoked and recovered 68-87% of the DMN values found when using the sidestream collection device applied in the other experiments. (Author abstract) (47 Refs)

104. UNDERESTIMATED: NITROSAMINES IN SMOKE

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*MMW; 124(4):12-13 1982*

Importance of nitrosamines (NA), especially dimethylnitrosamine, in the cigarette smoke is discussed. Smokers and passive smokers are equally exposed to NA in the same working and recreational areas. NA affect mostly lungs and liver causing cancer.

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